REMARKS

A. Claim Amendments

The foregoing amendments to pending claims are made primarily to correct grammatical errors in the claim language. Clarification of the treatment goals of the invention is also provided, both by amendments to pending claims and by the addition of new claims. For ease of reference, a clean set of claims without markups is appended to this document.

After amendment, Claims 18-19, 23-25 and 32-34 are pending. Claims 18, 19 and 23-25 are amended, while Claims 32-34 are new. Claims 20-22 are cancelled. In addition, consistent with the provisional election of species made herein, Claims 25-31 are withdrawn without prejudice to their representation in this application on withdrawal of the election of species requirement, on allowance of a generic linking claim, or in a subsequent related application.

No new matter is added by the proposed amendments, as illustrated below:

| Claim # | Amendment or Addition | Examples of Specification Support |
|---|---|---|
| 18 | Expression construct comprises an expressible polynucleotide rather than a "coding sequence"; changed to clarify nature of expression construct. | Page 17, line 10 through page 18, line 11; Example 3 (expressible "transgenes") |
| 18 | "...the dominant negative phospholamban increases cardiac contractility or cardiac relaxation" changed to "...accelerates SERCA2 mediated calcium ion transport in the treated myocytes to improve cardiac muscle contractility" to more specifically describe physiologic phenomenon targeted by invention. | Page 11, lines 7-15. |
| 19, 24-25 | "Coding sequence" changed to "expression construct" to make claim limitations consistent with antecedent basis in Claim 18. | Page 17, line 10 through page 18, line 11; Example 3 (expressible "transgenes") |

| Claim # | Amendment or Addition | Examples of Specification Support |
|---|---|---|
| 23 | "...mutated to imitate phosphorylation of phospholamban" changed to "a single or double point mutation in Domain Ia thereof, the effect of which is to diminish the inhibitory activity of the molecule on SERCA2" to clarify relationship between structure and function addressed by claims. | Page 3, lines 7-15 (domain structure of phospholamban); page 17, lines 10-20 (point mutations that diminish SERCA2 inhibitory activity). |
| 32 | Mutation identified in Claim 23 is R14E, S16N, S16E or K3E/R14E. | Page 17, lines 10-20. |
| 33 | "...mutated to imitate phosphorylation of phospholamban" changed to "a single or double point mutation in Domain II thereof, the effect of which is to diminish the inhibitory activity of the molecule on SERCA2" to clarify relationship between structure and function addressed by claims. | Page 3, lines 7-15 (domain structure of phospholamban); page 17, lines 10-20 (point mutations that diminish SERCA2 inhibitory activity). |
| 34 | Mutation identified in Claim 33 is V49A. | Page 17, lines 10-20. |

Entry of the foregoing amendments is respectfully requested.

B. Provisional Election of Species and Response to Restriction Requirement.

The Office Action requires an election of species as between increasing contractility or relaxation of cardiac muscle; among particular expression constructs (including, presumably, molecules encoded thereby); and among vectors utilized as expression constructs.

Election.

With traverse, Applicants provisionally elect the following:

--Increasing cardiac contractility utilizing the dominant-negative phospholambans (dnPLB) of the invention. (Claims 18-19, 23-25 and 31-34);

--Expression constructs which encode dnPLB molecules. (Claims 18-19, 23-25 and 31-34). Any suitable promoter known to those of ordinary skill in the art may be utilized in the expression construct. It is not clear whether restriction to expression constructs encoding a specific dnPLB molecule is also being required. If so, to expedite prosecution, Applicants would provisionally elect, with traverse, a dnPLB molecule having a mutation at amino acid 16 from serine to glutamic (S16E) (see, e.g., Specification at Example 5, page 29, lines 27-30), to produce a PLB molecule such as identified by SEQ. ID. Nos. 12 and 13. (Claims 23 and 32).

--Viral vectors (e.g., adeno- and adeno-associated viral DNA vectors) for use in the expression constructs of the invention. (Claims 19 and 24).

Traverse.

No reasons are set forth in the Office Action as to why the species identified in the restriction requirement are believed to be distinct inventions, for purposes of examination. As such, Applicants respectfully submit that no *prima facie* case supporting imposition of a restriction requirement under Section 121 has been made.

Nonetheless, to advance prosecution without delay, Applicants set forth their reasons for traversing the restriction requirement below. If, after considering these comments, the Examiner decides to maintain the requirement for election of species, Applicants respectfully request that the Examiner set forth the factual basis supporting that decision under Section 121 so it can be more fully addressed.

1. Election between impact on cardiac contractility and cardiac relaxation.

Contraction and relaxation of cardiac muscle are physiologically linked—one necessarily follows the other (see, e.g., Specification at page 12, lines 1-5 "..this increase in SR calcium content results in maintenance of normal calcium quantal release, thereby leading to maintenance

of normal contractility and relaxation."). As such, there is no logical basis upon which the two phenomena can be clearly divided. Applicants therefore respectfully submit that the requirement for an election between impacting contractility and relaxation in the invention is unwarranted, and should be withdrawn.

2. Election between expression constructs.

Applicants interpret this aspect of the restriction requirement as directing selection of a phospholamban (PLB) molecule for expression from an expression construct. To that end, the dominant-negative (dn) PLB molecules of the invention have been provisionally elected, versus the antisense molecules of Claims 25-31.

However, Applicants submit that any further restriction between the dnPLB molecules disclosed is not warranted. Each dnPLB molecule disclosed disrupts the physiological interaction between endogenous PLB and SERCA2, thereby modifying (albeit to different degrees) the set point of *in vivo* contractility and relaxation targeted by the invention (see, e.g., page 17, lines 23-28, regarding the activity of the molecules of the invention; Figure 5 (comparison to wild-type PLB activity) and Figure 6a (impact on PLB protein content in myocytes treated with various dnPLB molecules of the invention).

It is this effect, rather than the particular structure of the molecules used to accomplish it, that is presently claimed. Therefore, as all of the dnPLB molecules disclosed and claimed accomplish the claimed goals of the invention, election among them should not be required.

3. Election between expression vectors.

Applicants interpret this requirement as directing them to select between classes of potential vectors for use in the heart; e.g., viral vectors, viral DNA vectors, viral RNA vectors, plasmids, etc. Of those choices, Applicants have provisionally elected viral vectors.

However, those of ordinary skill in the art are aware of all of the potential choices for use as recombinant expression vectors, including a number that have actually been used in the heart. The characteristics of those vectors, including the advantages and disadvantages presented by each, are also well-known. See, for example, U.S. Patent No. 5,797,870 (viral vectors, including adenoviral vectors and adeno-associated virus vectors, identified as constructs for delivery of genes to the heart ); U.S. Patent No. 5,919,449 (treatment of congestive heart failure using viral expression vectors); and, U.S. Patent 6,162,796 (comparison of AAV to adenovirus and other retroviruses for use in the heart). Hence, skilled artisans will be readily able to select appropriate vectors for use in the methods of the invention.

To varying degrees, such vectors can be reasonably expected to produce expression of the dnPLB molecules disclosed, to accomplish the disruption between PLB and SERCA2's interaction targeted by the claimed invention. It is this effect, rather than the particular structure of the molecules (and vectors for their expression) used to accomplish it, that is presently claimed. Therefore, election among particular vectors that may all be used to that end should not be required.

CONCLUSION

For all of the foregoing reasons, Applicants respectfully submit that the requirement for election of the species discussed above should be reconsidered and withdrawn.

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check

being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872.

If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Respectfully submitted,

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By _____

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